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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,462	04/25/2001	Barbara A. Foster	PC10583ADAM	8327

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/843,462	FOSTER ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 September 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *1, 4-8, and 20*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

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ADVISORY ACTION

Amendment Entry

1. Applicants' response to the Final action mailed 17 May 2004 is acknowledged. (Filed 17 September 2004). In the amendment filed therein claim 1 was modified. Claims 2, 3, 9, 19, and 21-23 were canceled without prejudice. Currently claims 1, 4-8 and 20 are pending and under consideration.

2. All rejections of record have been maintained.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 4-7, and 20 are (previously claims 1-7 and 20) rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350).

Wen et al. teach an ELISA (enzyme linked immuosorbent assay) to detect $p110^{RB}$ (retinoblastoma protein). ELISA methods are taught in the instant specification (see page 6, figure 1) A coating antibody (anti-retinoblastoma protein (Rb) capture antibody) in combination with a 3C8 monoclonal antibody (anti-Rb primary antibody) is used to measure the retinoblastoma protein. See page 235, Section 3.3

Wen et al. differ from the instant invention in not specifically teaching the correlation of retinoblastoma protein to cyclin-dependent CDK activity.

However, Juan et al. disclose a method to measure the in situ phosphorylation state of retinoblsatoma protein (pRb). This is accomplished by employing dual antibodies simultaneously to detect pRb. One antibody specifically detects underphosphorylated forms of the protein (pRb^{P-}) and the other reacts with total (pRb^{T}). The conjugation of these anti-pRb mAbs with fluorochromes of different color, allows for multiparametered flow cytometry analysis. See page 105, 1st paragraph, 1st column. In the method human peripheral blood lymphocytes in culture are contacted with anti-pRb^{T}conjugated to CY-Chrome and anti-pRb^{P-} conjugated with FITC. (Please see page 105, 1st column, 2nd paragraph). The fluorescence measurement can be utilized to detect agents that target CDK4 activity or other CKDs activity in pRb phosphorylation activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure CDK activity as taught by Juan et al. with the retinoblastoma protein detection method of Wen et al., because Juan et al. taught that assays to detect retinoblastoma proteins "could be applied for screening ...CDKs and monitoring retinoblastoma phosphorylation". See abstract.

Juan et al. also taught that the function of pRb is affected by its phosphorylation at serine and threonine residues by the cyclin-dependent kinases. Page 104, 2nd column 1st paragraph.

One having ordinary skill in the art would have been motivated to correlate CDK activity in retinoblastoma protein detection in order to more obtain information with respect to the function of the protein.

Wen et al. in view of Juan et al. differ from the instant invention in not specifically teaching the measurement of CDK2 and CDK4 activity with a capture antibody recognizing site specific phosphorylation sited like Ser612 or Ser780.

However, Watanabe et al. disclose antibodies to detect the phosphorylation of retinoblastoma protein (pRb). Applicant's Rb protein. The formed complex was further employed to measure Cdk2 and Cdk4 kinase activities. See abstract. The reference teaches that pRb contains more than 12 phosphorylation sites at serine or threonine, and is phosphorylated by cyclin-dependent kinases (Cdks) in a cell cyclin-dependent manner. Page 342, 2nd column. Antibodies directed to Ser780 and Ser612 are taught on page 343 –2.3 Antibodies.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure Cyclin E/Cdk2 and Cyclin D/Cdk4 activity with known phosphorylation site-specific antibodies as taught by Watanabe et al. in the retinoblastoma protein detection method of Wen et al. in view of Juan et al., because Watanabe et al. taught that "recently, consensus motifs for phosphorylation by cyclin D/Cdk4 and cyclin E/Cdk2 were determined and antibodies against pRb phosphoyalted sites were prepared".... by Kitagawa et al. (page 343, 1st column, 2nd paragraph). Juan et al. further taught "little is known about the site specific phosphorylation of pRb in vivo during the differentiation process". (page 343, 1st column, 2nd paragraph).

Therein one having ordinary skill in the art would have been motivated to employ the known Cyclin E/Cdk2 and Cyclin D/Cdk4 antibodies directed to known sites of the retinoblastoma protein (pRb) in order to understand cyclin dependent kinase activity (cdks) in a sample. The knowledge of site specific-antibodies enhanced sensitivity with respect to where the pRb protein is being phosphorylated, therefore none relevant sites are not evaluated giving more accurate and precise detection.

II. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) as applied to claims 1-7 and 20 above, and further in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187).

Please see Wen et al. in view of Juan et al. and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) as set forth above.

Wen et al. in view of Juan et al. and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) differ from the instant invention in not specifically teaching the detection assay in test plates/micro titer plates.

However, Maggio disclose enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase/test plate. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (micro titer plates). See page 186.

Wen et al., Juan et al., Watanabe et al., and Maggio are analogous art because they are from the same field of endeavor, all four inventions teach methods immunoassay methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use micro titer plates as taught by Maggio in the assay method to detection retinoblastoma protein of Wen et al. in view of Juan et al. and further in view of Watanabe et al. because Maggio taught that micro plates or micro titer plates "are very convenient to wash thereby reducing labor in assay procedures". Page 186, last line.

Response to Argument

4. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that Wen teaches an assay for detecting total Rb and does not disclose specific Rb residues targeted for assessing CDK2 activity. This argument was carefully considered but not found persuasive because Wen was merely cited to show dual antibody methods measuring Rb. Further, Wen is cited in combination with Watanabe et al. and Watanabe et al. is relied on for teaching the specific Rb residues targeted for assessing CDK2 activity. See abstract and pages 343–344 Antibodies. While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. In re Lyons, 364 F.2d1005, 150 USPQ 741, 746 (CCPA 1966).

Applicant argues that Juan discloses an assay monitoring Rb phosphorylation by incubating cells with dual fluorochrome tagged antibodies resulting in the measurement of dual readouts, while the instant invention measures a single readout in an ELISA based dual antibody-complex assay. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., single readout in an ELISA based dual antibody-complex assay) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is also noted that the instant claims uses open language "comprising" and therefore would not be limited to single readout measurements.

The Declaration of Barbara A. Foster and Farzan Rastinejad filed on 09 May 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the Watanabe et al., Brain Research 842:342-50, 1999 reference.

While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The Declaration is not accompanied with exhibits of drawings or records, or photocopies thereof. Please see 37 CFR 1.131 Affidavit or declaration of prior invention.

b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence
satisfactorily explained.

In support of the Declaration, Applicant has provided a fax copy of a Patent Application submitted on June 10, 1999 to the Pfizer's New York Patent Department. Therein proving a conception and reduction to practice date of June 10, 1999. This was considered but not found persuasive because Watanabe et al. were cited to teach Cdk2 and Cdk4 site-specific antibodies. Watanabe et al. teach this concept as disclosed by M.Kitagawa and Y.Taya in 1996. See page 343 – 1st column 2nd paragraph and reference #15 on page 349. The concept taught by Watanabe et al. as disclosed by Kitagawa and Taya was reduced to practice as early as 1996 before Applicants June 10, 1999 date.

Applicant has amended the instant claims to eliminate Ser780 and CDK4 to overcome the teachings of M.Kitagawa and Y.Taya in 1996. The arguments and amendments were considered but not found persuasive because Watanabe et al. still reads on CDK2 activity at the cited Rb phosphorylated specific sites. Watanabe et al. teach antibodies to Ser612, which is an active, cite for cdk2 phosphorylation (activity).

See anti-pRb-P-Ser612 on page 343.

Watanabe et al. also discuss the preferential phosphorylation cite of Ser612 by cyclin E/Cdk2 in previous cited art. See page 345 section 3.3 lines 6-7. In one reference to Zarkowska and Mittnacht (39) CDK2 activity at Thr821, Thr373, Ser795, Ser612, and Thr5. See page 12743 – Summary of phosphorylation analysis. Zarkowska and Mittnacht (39), Vol.272, No.19, May 9, 1997, 12738-12746. Accordingly, the rejection is maintained.

Applicant contends that the method do not teach phosphorylated Rb and CDK activity via Rb phosphorylation at specific residues by CDK (capture antibody). This argument was carefully considered but not found persuasive because Watanabe et al. teach Cdk2 and Cdk4 activity via phosphoylated Rb sites including Ser780 and Ser612 as recited in the instant claims. See page 343 2nd column - Antibodies.

The rejections including Watanabe et al. (Brian Research, 842, 1999, pages 342-350) and Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187) are maintained in view of the response above. Accordingly the rejections are maintained.

The rejections above teach methods employing dual antibodies to Rb in various states (phosphorylated, underphosphorylated, and irrespective of phosphorylation) as a means for measuring CDK activity (Wen et al. in view of Juan et al.). Although the methods do not reciting the capture antibodies used by Applicant the commercially available antibody reagents are taught by Watanabe et al. The rejections including Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187) are maintained in view of the response above. Accordingly the rejections are maintained.

5. For reasons aforementioned, no claims are allowed.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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